LISTING OF THE CLAIMS

1. (Currently amended) A method of identifying a compound that modulates nuclear receptor activity, ~~said~~ the method comprising:

modeling a test ~~compounds~~ compound that ~~fit~~ fits spatially into a the nuclear receptor ligand binding domain ~~of interest~~ using an atomic structural model of a portion of the estrogen receptor α ligand binding domain ~~or portion thereof~~, wherein said atomic structural model comprises atomic coordinates of helix 12 of the ligand binding domain, and of a coactivator binding site, and further comprises atomic coordinates of a coactivator bound to the coactivator binding site; and

screening said test ~~compounds~~ compound in an assay characterized by binding of a test compound to the ligand binding domain, ~~and~~ thereby

identifying a test compound that modulates nuclear receptor activity~~, wherein said atomic structural model comprises atomic coordinates of amino acid residues corresponding to residues of human estrogen receptor α Met343, Leu346, Ala350, Glu353, Leu384, Leu387, Leu391, Arg394, Phe404, Met421, Leu428, Gly521, His524, Leu525 and Met528~~.

2. (Currently amended) The method of Claim 1 wherein the atomic structural model additionally comprises coordinates of amino acid residues that correspond to human estrogen receptor α residues Met343, Leu346, Ala350, Glu353, Leu384, Leu387, Leu391, Arg394, Phe404, Met421, Leu 428, Gly 521, His524, Leu525 and Met528, and wherein said test compound interacts with at least one of said amino acid residues.

3. (Original) The method of Claim 1 wherein the test compound is an agonist and nuclear receptor activity is measured by binding of a coactivator to the coactivator binding site.

4. (Currently amended) The method of Claim 1 wherein the test compound is an antagonist and nuclear receptor activity is measured by ~~the unwinding~~ a change in position of helix 12 so that helix 12 contacts the coactivator binding site thereby inhibiting coactivator binding.

5. (Currently amended) The method of Claim 1 wherein the test compound is an antagonist and nuclear receptor activity is measured by [[the]] blocking of coactivator binding.

6. (Original) The method of Claim 1 wherein said screening is in vitro.

7. (Original) The method of Claim 6 wherein said screening is high throughput screening.

8. (Original) The method of Claim 1 wherein said test compound is from a library of compounds.

9. (Currently amended) The method of Claim 1 wherein said test compound is a small organic molecule, a peptide, or a peptidomimetic.

10. (Currently amended) The method of Claim 1 ~~which further~~ wherein the modeling comprises ~~the step of~~ providing the atomic coordinates of the portion of the estrogen receptor α ligand binding domain ~~or portion thereof~~ to a computerized modeling system~~, prior to said modeling step~~.

11. (Original) The method of Claim 1 wherein said nuclear receptor is selected from the group consisting of estrogen receptors, thyroid receptors, retinoid receptors, glucocorticoid receptors, progestin receptors, mineralocorticoid receptors, androgen receptors, peroxisome receptors and vitamin D receptors.

12. (Original) The method of Claim 11 wherein said nuclear receptor is an estrogen receptor.

13. (Original) The method of Claim 12 wherein said estrogen receptor is the estrogen receptor α.

14. (Currently amended) A method of identifying a compound that modulates ligand binding to a nuclear receptor, ~~said~~ the method comprising:

modeling a test ~~compounds~~ compound that ~~fit~~ fits ~~spacially~~ spatially into a the nuclear receptor ligand binding domain ~~of interest~~ using an atomic structural model of a portion of the estrogen receptor α ligand binding domain ~~or portion thereof~~, wherein the atomic structural model comprises atomic coordinates of helix 12 of the ligand binding domain, and of a coactivator binding site, and further comprises atomic coordinates of a coactivator bound to the coactivator binding site; and

screening said test ~~compounds~~ compound in an assay characterized by binding of ~~a~~ the test compound to the ligand binding domain, ~~and~~ thereby identifying a test compound that modulates ligand binding to said nuclear receptor~~, wherein said atomic structural model comprises atomic coordinates of amino acid residues corresponding to residues of human estrogen receptor α Met343, Leu346, Ala350, Glu353, Leu384, Leu387, Leu391, Arg394, Phe404, Met421, Leu428, Gly521, His524, Leu525 and Met528~~.

15. (Currently amended) The method of Claim 14 wherein the atomic structural model additionally comprises coordinates of amino acid residues that correspond to human estrogen receptor α residues Met343, Leu346, Ala350, Glu353, Leu384, Leu387, Leu391, Arg394, Phe404, Met421, Leu 428, Gly 521, His524, Leu525 and Met528, and wherein said test compound interacts with at least one of said amino acid residues.

16. (Original) The method of Claim 14 wherein said nuclear receptor is selected from the group consisting of estrogen receptors, thyroid receptors, retinoid receptors, glucocorticoid receptors, progestin receptors, mineralocorticoid receptors, androgen receptors, peroxisome receptors and vitamin D receptors.

17. (Original) The method of Claim 16 wherein said nuclear receptor is an estrogen receptor.

18. (Original) The method of Claim 17 wherein said estrogen receptor is the estrogen receptor α.

19. (Original) The method of Claim 14 wherein said screening is in vitro.

20. (Original) The method of Claim 19 wherein said screening is high throughput screening.

21. (Original) The method of Claim 14 wherein said test compound is from a library of compounds.

22. (Currently amended) The method of Claim 14 wherein said test compound is an agonist ~~or antagonist~~ of ligand binding that facilitates binding of a coactivator to the coactivator binding site.

23. (Currently amended) The method of Claim 14 wherein said test compound is a small organic molecule, a peptide, or a peptidomimetic.

24. (Currently amended) A method for identifying an agonist ~~or antagonist~~ of ligand binding to ~~a nuclear~~ an estrogen receptor, ~~said~~ the method comprising ~~the steps of~~:

~~providing the atomic coordinates of the estrogen receptor α ligand binding domain or portion thereof to a computerized modeling system, wherein said atomic coordinates are of the amino acid residues corresponding to residues of human estrogen receptor α Met343, Leu346, Ala350, Glu353, Leu384, Leu387, Leu391, Arg394, Phe404, Met421, Leu428, Gly521, His524, Leu525 and Met528;~~

modeling a test ~~compounds~~ compound which ~~fit~~ fits ~~spacially~~ spatially into an atomic structural model of the estrogen receptor α ligand binding domain, wherein the atomic structural model comprises atomic coordinates of helix 12 of the ligand binding domain, and of a coactivator binding site, and further comprises atomic coordinates of a coactivator bound to the coactivator binding site; and

~~identifying~~ screening in an assay for ~~nuclear~~ estrogen receptor activity a compound which increases ~~or decreases~~ the activity of the ~~nuclear~~ estrogen receptor by binding th ligand binding domain of ~~said nuclear~~ the estrogen receptor, ~~whereby~~ thereby identifying an agonist ~~or antagonist~~ of ligand binding ~~is identified~~.

25. (Currently amended) The method of Claim 24 wherein the atomic structural model additionally comprises coordinates of amino acid residues that correspond to human estrogen receptor α residues Met343, Leu346, Ala350, Glu353, Leu384, Leu387, Leu391, Arg394, Phe404, Met421, Leu428, Gly521, His524, Leu525 and Met528, and wherein said test compound interacts with at least one of said amino acid residues.

26. (Cancelled)

27. (Cancelled)

28. (Cancelled)

29. (Currently amended) A method of modulating nuclear receptor activity in a mammal by administering to a mammal in need thereof a sufficient amount of a compound that fits spatially and preferentially into a ligand binding domain of a the nuclear receptor ~~of interest~~, ~~where~~

wherein said compound is designed by a computational method that involves fitting an atomic model of the compound into an atomic structural model of the ligand binding domain of the estrogen receptor that comprises atomic coordinates of helix 12 of the ligand binding domain, and of a coactivator binding site, and further comprises atomic coordinates of a coactivator bound to the coactivator binding site, so ~~as to distort~~ that the molecule interacts with at least one amino acid residue corresponding to residues of human estrogen receptor α Met343, Leu346, Ala350, Glu353, Leu384, Leu387, Leu391, Arg394, Phe404, Met421, Leu428, Gly521, His524, Leu525 and Met528.

30. (Currently amended) The method of Claim 29 wherein the test compound is an antagonist that causes a change in position of helix 12 so that helix 12 contacts the coactivator binding site thereby inhibiting coactivator binding ~~at least one amino acid residue corresponds to residues Met343, Met421, His524, Leu525 and Met528~~.

31. (Original) The method of Claim 29 wherein said nuclear receptor is selected from the group consisting of estrogen receptors, thyroid receptors, retinoid receptors, glucocorticoid receptors, progestin receptors, mineralocorticoid receptors, androgen receptors, peroxisome receptors and vitamin D receptors.

32. (Original) The method of Claim 31 wherein said nuclear receptor is an estrogen receptor.

33. (Original) The method of Claim 32 wherein said estrogen receptor is the estrogen receptor α.

34. (Currently amended) A machine-readable data storage medium~~, comprising a data storage material~~ encoded with machine readable data which, when using a machine programmed with instructions for using said data, is capable of displaying a graphical three-dimensional representation of a molecular complex, wherein the data comprises coordinates of: a portion of an estrogen receptor ligand binding domain, including helix 12 of the ligand binding domain; a coactivator binding site; and a compound bound to ~~a nuclear~~ the estrogen receptor ~~ligand~~ coactivator binding ~~domain~~ site ~~comprising structure coordinates of amino acids corresponding to human estrogen receptor α Met343, Leu346, Ala350, Glu353, Leu384, Leu387, Leu391, Arg394, Phe404, Met421, Leu428, Gly521, His524, Leu525 and Met528 or a homologue of said~~

~~molecular complex, wherein said homologue comprises a ligand binding domain that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å.~~

35. (Currently amended) The machine-readable data storage medium of Claim 34 wherein the atomic structural model additionally comprises coordinates of amino acid residues that correspond to human estrogen receptor α residues Met343, Leu346, Ala350, Glu353, Leu384, Leu387, Leu391, Arg394, Phe404, Met421, Leu428, Gly521, His524, Leu525 and Met528.

36. (Cancelled)

37. (Cancelled)

38. (Cancelled)

39. (Currently amended) The machine-readable data storage medium of Claim 34 wherein said molecular complex is defined by the set of structure coordinates depicted in Appendix 1 ~~or Appendix 2~~, or a homologue of said molecular complex, said homologue having a root mean square deviation from the coordinates of the backbone atoms of said ~~amino acids~~ ligand binding domain of not more than 1.5Å.

40. (Original) A machine-readable data storage medium comprising a data storage material encoded with a first set of machine readable data which, when combined with a second set of machine readable data, using a machine programmed with instructions for using said first set of data and said second set of data, can determine at least a portion of the structure coordinates corresponding to the second set of machine readable data, wherein: said first set of data comprises a Fourier transform of at least a portion of the structural coordinates selected from the group consisting of coordinates depicted in Appendix 1 or Appendix 2; and said second set of data comprises an X-ray diffraction pattern of a molecule or molecular complex.

41. (Currently amended) [[A]] The machine-readable data storage medium of Claim 40 wherein said nuclear receptor is selected from the group consisting of estrogen receptors, thyroid receptors, retinoid receptors, glucocorticoid receptors, progestin receptors, mineralocorticoid receptors, androgen receptors, peroxisome receptors and vitamin D receptors.

42. (Original) The machine-readable data storage medium of Claim 41 wherein said nuclear receptor is an estrogen receptor.

43. (Original) The machine-readable data storage medium of Claim 42 wherein said estrogen receptor is the estrogen receptor α.

44. (Currently amended) A cocrystal comprising: ~~of a nuclear~~ a portion of an estrogen receptor ligand binding domain; ~~comprising~~ an agonist bound to the ligand binding domain; and a molecule bound to ~~the~~ a coactivator binding site of the ~~nuclear~~ estrogen receptor~~, wherein said crystal defracts with at least 2.03Å resolution~~.

45. (Original) The cocrystal of Claim 44 wherein said nuclear receptor is the estrogen receptor α.

46. (Original) The cocrystal of Claim 45 wherein said estrogen receptor α is human.

47. (Currently amended) The cocrystal of Claim 46 wherein said molecule is a peptide.

48. (Original) The cocrystal of Claim 47 wherein said peptide comprises a NR-box amino acid sequence or derivative thereof.

49. (Currently amended) A cocrystal ~~of a nuclear~~ comprising: a portion of an estrogen receptor ~~comprising~~ ligand binding domain and an antagonist bound to the ligand binding domain ~~of the nuclear receptor~~, wherein said ~~crystal~~ ~~defracts~~ cocrystal diffracts with at least 1.9Å resolution.

50. (Currently amended) The cocrystal of Claim ~~49~~ 44 wherein ~~said nuclear receptor is the estrogen receptor α~~ said cocrystal diffracts with at least 2.03 Å resolution.

51. (Currently amended) The cocrystal of Claim 50 wherein said estrogen receptor [[α]] is human.

52. (Currently amended) A computational method of designing a nuclear receptor ligand ~~where at least one amino acid residue of a nuclear receptor LBD that corresponds to human estrogen receptor α Met343, Leu346, Ala350, Glu353, Leu384, Leu387, Leu391, Arg394, Phe404, Met421, Leu428, Gly521, His524, Leu525 and Met528, interacts with at least one first chemical moiety of said ligand~~, comprising: ~~the step of selecting at least one chemical modification of said first chemical moiety to produce a second chemical moiety with a structure~~

~~to either decrease or increase an interaction between said interacting amino acid and said second chemical moiety compared to said interaction between said interacting amino acid and said first chemical moiety~~

fitting an atomic model of the ligand into an atomic structural model of the ligand binding domain of the estrogen receptor, wherein the atomic structural model comprises atomic coordinates of helix 12 of the ligand binding domain, and of a coactivator binding site, and further comprises atomic coordinates of a coactivator bound to the coactivator binding site; and

carrying out a chemical modification of a first chemical moiety of said ligand that interacts with the ligand binding domain, to produce a second chemical moiety.

53. (Currently amended) The method of Claim 52 wherein the atomic structural model additionally comprises coordinates of at least one amino acid residue that corresponds to human estrogen receptor α residues Met343, Leu346, Ala350, Glu353, Leu384, Leu387, Leu391, Arg394, Phe404, Met421, Leu428, Gly521, His524, Leu525 and Met528, and wherein said first chemical moiety interacts with at least one of said amino acid residues.

54. (Currently amended) The method of Claim 52 further comprising determining a change in interaction between said interacting amino acid and said ligand after the chemical modification of said first chemical moiety.

55. (Currently amended) The method of Claim ~~52~~ 54 wherein said chemical modification enhances an interaction selected from the group consisting of: hydrogen bonding interaction, charge interaction, hydrophobic interaction, ~~Van Der~~ van der Waals interaction or dipole interaction between said second chemical moiety and one of said ~~interacting~~ amino acid residues compared to said first chemical moiety ~~and said interacting amino acid~~.

56. (Currently amended) The method of Claim ~~52~~ 54 wherein said chemical modification reduces an interaction selected from the group consisting of: hydrogen bonding interaction, charge interaction, hydrophobic interaction, ~~Van Der~~ van der Waals interaction or dipole interaction between said second chemical moiety and one of said ~~interacting~~ amino acid residues compared to said first chemical moiety ~~and said interacting amino acid~~.

57. (Original) The method of Claim 52 wherein said nuclear receptor is selected from the group consisting of estrogen receptors, thyroid receptors, retinoid receptors, glucocorticoid

receptors, progestin receptors, mineralocorticoid receptors, androgen receptors, peroxisome receptors and vitamin D receptors.

58. (Original) The method of Claim 57 wherein said nuclear receptor is an estrogen receptor.

59. (Currently amended) The method of Claim ~~52~~ 57 wherein the estrogen receptor is the estrogen receptor α.

60. (Original) The method of Claim 59 wherein the ligand is an agonist.

61. (Original) The method of Claim 60 wherein the ligand is selected from the group consisting of 17β-estradiol, diethylstilbestrol, moxestrol, mesohexestrol, coumestrol, Δ^9-THC, o,p-DDT, zearalenone and kepone.

62. (Original) The method of Claim 61 wherein the ligand is 17β-estradiol, and the first chemical moiety is a free carbon of the A' ring located at a position selected from the group consisting of C6α, C7α, C12α, C15α, C16α and C17α.

63. (Original) The method of Claim 59 wherein the ligand is an antagonist.

64. (Original) The method of Claim 63 wherein the ligand is selected from the group consisting of ICI 164,384 and EM800.

65. (Original) The method of Claim 59 wherein the ligand is a selective estrogen receptor modulator.

66. (Original) The method of Claim 65 wherein the ligand is selected from the group consisting of tamoxifen, raloxifene and GW5638.

67. (Currently amended) A method of modulating nuclear receptor activity in a mammal by administering to a mammal in need thereof a sufficient amount of a ligand that fits spatially and preferentially into a ligand binding domain of a nuclear receptor of interest, wherein said ligand is designed by a computational method ~~where at least one amino acid residue of a nuclear receptor ligand binding domain that corresponds to human estrogen receptor α Met343, Leu346, Ala350, Glu353, Leu384, Leu387, Leu391, Arg394, Phe404, Met421, Leu428, Gly521, His524,~~

~~Leu525 and Met528, interacts with at least one first chemical moiety of said ligand,~~ comprising: ~~the step of selecting at least one chemical modification of said first chemical moiety to produce a second chemical moiety with a structure to either decrease or increase an interaction between said interacting amino acid and said second chemical moiety compared to said interaction between said interacting amino acid and said first chemical moiety~~

fitting an atomic model of the ligand into an atomic structural model of the ligand binding domain of the estrogen receptor, wherein the atomic structural model comprises atomic coordinates of helix 12 of the ligand binding domain, and of a coactivator binding site, and further comprises atomic coordinates of a coactivator bound to the coactivator binding site; and

carrying out a chemical modification of a first chemical moiety of said ligand that interacts with the ligand binding domain, to produce a second chemical moiety.

68. (Currently amended) The method of Claim 67 wherein the atomic structural model additionally comprises coordinates of at least one amino acid residue that corresponds to human estrogen receptor α residues Met343, Leu346, Ala350, Glu353, Leu384, Leu387, Leu391, Arg394, Phe404, Met421, Leu428, Gly521, His524, Leu525 and Met528, and wherein said first chemical moiety interacts with at least one of said amino acid residues.

69. (Original) The method of Claim 67 wherein said ligand is an antagonist.

70. (Original) The method of Claim 67 wherein said ligand is an agonist.

71. (Currently amended) The method of Claim 70 ~~which~~ further ~~comprises~~ comprising administering a coactivator mimic designed by a computational method that comprises: fitting an atomic model of the mimic into the atomic structural model where at least one amino acid residue of a the nuclear receptor coactivator binding site that corresponds to human estrogen receptor α helix 3 residues Leu354, Val355, Met357, Ile358, Ala361 and Lys362, helix 4 residue Phe367, helix 5 residues Gln375, Val376, Leu379 and Glu380, helix 6 residue Trp383, and helix 12 residues Asp538, Leu539, Glu542, Met543 and Leu544, interacts with at least one first chemical moiety of said coactivator mimic, ~~comprising;~~ and ~~the step of~~ selecting at least one chemical modification of said first chemical moiety to produce a second chemical moiety ~~with~~ that has a structure to either decrease or increase an interaction between said coactivator binding site ~~interacting amino acid~~ and said second chemical moiety compared to ~~said~~ an

interaction between said coactivator binding site ~~interacting amino acid~~ and said first chemical moiety.

72. (New) The method of claim 1 wherein the test compound is an antagonist that permits helix 12 to bind to a static region of the coactivator binding site.

73. (New) The method of claim 1 wherein the atomic structural model has coordinates presented in Appendix 1.

74. (New) The method of claim 1 wherein the atomic structural model is of a homolog of the portion of the estrogen α receptor ligand binding domain, wherein the homolog comprises a ligand binding domain that has a root mean square deviation of not more than 1.5 Å from the backbone atoms of the amino acid residues of the atomic structural model of Appendix 1.

75. (New) The method of Claim 1 wherein the atomic structural model additionally comprises coordinates of amino acid residues that correspond to human estrogen receptor α residues Ala350, Glu353, Leu387, Leu391, Arg394, and Phe404, wherein said residues lie on a surface of a binding pocket in the ligand binding domain, and wherein said test compound is an agonist that interacts with at least one of said amino acid residues.

76. (New) The method of Claim 1 wherein the atomic structural model additionally comprises coordinates of amino acid residues that correspond to human estrogen receptor α residues Met343, Leu346, Gly 521, His524, Leu525, and either residues Met421 and Met528, or residues Met388 and Ile424, wherein said residues lie on a surface of a binding pocket in the ligand binding domain, and wherein said test compound is an agonist that interacts with at least one of said amino acid residues.

77. (New) The method of Claim 1 wherein the atomic structural model additionally comprises coordinates of amino acid residues that correspond to human estrogen receptor α residues Met343, Leu346, Thr347, Ala350, Trp383, Leu384, Leu387, and Leu525, wherein said residues lie on a surface of a binding pocket in the ligand binding domain, and wherein said test compound is an antagonist that interacts with at least one of said amino acid residues.

78. (New) The method of Claim 1 wherein the atomic structural model additionally comprises coordinates of amino acid residues that correspond to human estrogen receptor α

residues Met343, Leu346, Met421, Ile 424, Gly 521, His524, and Leu525, wherein said residues lie on a surface of a binding pocket in the ligand binding domain, and wherein said test compound is an antagonist that interacts with at least one of said amino acid residues.

79. (New) The method of claim 1 wherein the atomic structural model is experimentally derived.

80. (New) The method of claim 79 wherein the atomic structural model has a resolution of at least 2.03 Å.

81. (New) The method of claim 4 wherein the modeling further comprises comparing a second atomic structural model of a portion of the estrogen receptor α ligand binding domain with the atomic structural model, wherein the second atomic structural model comprises atomic coordinates of amino acid residues of helix 12 of the ligand binding domain and of a coactivator binding site, wherein the helix 12 contacts the coactivator binding site, and further comprises atomic coordinates of an antagonist molecule bound to the ligand binding domain.

82. (New) The method of claim 81 wherein the second atomic structural model is experimentally derived.

83. (New) The method of claim 82 wherein the second atomic structural model has a resolution of at least 1.90 Å.

84. (New) The method of claim 81 wherein the second atomic structural model has coordinates presented in Appendix 2.

85. (New) The method of claim 81 wherein the second atomic structural model is of a homolog of the portion of the estrogen α receptor ligand binding domain, wherein the homolog comprises a ligand binding domain that has a root mean square deviation of not more than 1.5 Å from the backbone atoms of the amino acid residues of the atomic structural model of Appendix 2.

86. (New) The method of Claim 14 wherein the test compound is an antagonist that permits helix 12 to bind to a static region of the coactivator binding site.

87. (New) The method of claim 14 wherein the atomic structural model has coordinates presented in Appendix 1.

88. (New) The method of claim 14 wherein the atomic structural model is of a homolog of the portion of the estrogen α receptor ligand binding domain, wherein the homolog comprises a ligand binding domain that has a root mean square deviation of not more than 1.5 Å from the backbone atoms of the amino acid residues of the atomic structural model of Appendix 1.

89. (New) The method of Claim 14 wherein the atomic structural model additionally comprises coordinates of amino acid residues that correspond to human estrogen receptor α residues Ala350, Glu353, Leu387, Leu391, Arg394, and Phe404, wherein said residues lie on a surface of a binding pocket in the ligand binding domain, and wherein said test compound is an agonist that interacts with at least one of said amino acid residues.

90. (New) The method of Claim 14 wherein the atomic structural model additionally comprises coordinates of amino acid residues that correspond to human estrogen receptor α residues Met343, Leu346, Gly 521, His524, Leu525, and either residues Met421 and Met528, or residues Met388 and Ile424, wherein said residues lie on a surface of a binding pocket in the ligand binding domain, and wherein said test compound is an agonist that interacts with at least one of said amino acid residues.

91. (New) The method of Claim 14 wherein the atomic structural model additionally comprises coordinates of amino acid residues that correspond to human estrogen receptor α residues Met343, Leu346, Thr347, Ala350, Trp383, Leu384, Leu387, and Leu525, wherein said residues lie on a surface of a binding pocket in the ligand binding domain, and wherein said test compound is an antagonist that interacts with at least one of said amino acid residues.

92. (New) The method of Claim 14 wherein the atomic structural model additionally comprises coordinates of amino acid residues that correspond to human estrogen receptor α residues Met343, Leu346, Met421, Ile 424, Gly 521, His524, and Leu525, wherein said residues lie on a surface of a binding pocket in the ligand binding domain, and wherein said test compound is an antagonist that interacts with at least one of said amino acid residues.

93. (New) The method of Claim 14 wherein the modeling comprises providing the atomic coordinates of the portion of the estrogen receptor α ligand binding domain to a computerized modeling system.

94. (New) The method of claim 14 wherein the atomic structural model is experimentally derived.

95. (New) The method of claim 94 wherein the atomic structural model has a resolution of at least 2.03 Å.

96. (New) The method of Claim 14 wherein the test compound is an antagonist that causes a change in position of helix 12 so that helix 12 contacts the coactivator binding site thereby inhibiting coactivator binding.

97. (New) The method of claim 96 wherein the modeling further comprises comparing a second atomic structural model of a portion of the estrogen receptor α ligand binding domain with the atomic structural model, wherein the second atomic structural model comprises atomic coordinates of amino acid residues of helix 12 of the ligand binding domain and of a coactivator binding site, wherein the helix 12 contacts the coactivator binding site, and further comprises atomic coordinates of an antagonist molecule bound to the ligand binding domain.

98. (New) The method of claim 97 wherein the second atomic structural model is experimentally derived.

99. (New) The method of claim 98 wherein the second atomic structural model has a resolution of at least 1.90 Å.

100. (New) The method of claim 97 wherein the second atomic structural model has coordinates presented in Appendix 2.

101. (New) The method of claim 97 wherein the second atomic structural model is of a homolog of the portion of the estrogen α receptor ligand binding domain, wherein the homolog comprises a ligand binding domain that has a root mean square deviation of not more than 1.5 Å from the backbone atoms of the amino acid residues of the atomic structural model of Appendix 2.

102. (New) The method of Claim 24 wherein said screening is in vitro.

103. (New) The method of Claim 102 wherein said screening is high throughput screening.

104. (New) The method of Claim 24 wherein said test compound is from a library of compounds.

105. (New) The method of Claim 24 wherein said test compound facilitates binding of a coactivator to the coactivator binding site.

106. (New) The method of Claim 24 wherein said test compound is a small organic molecule, a peptide, or peptidomimetic.

107. (New) The method of Claim 24 wherein the test compound is an agonist that permits the coactivator molecule to bind to a static region of the coactivator binding site.

108. (New) The method of Claim 24 wherein the modeling comprises providing the atomic coordinates of the portion of the estrogen receptor α ligand binding domain to a computerized modeling system.

109. (New) The method of Claim 24 wherein the atomic structural model additionally comprises coordinates of amino acid residues that correspond to human estrogen receptor α residues Ala350, Glu353, Leu387, Leu391, Arg394, and Phe404, wherein said residues lie on a surface of a binding pocket in the ligand binding domain, and wherein said test compound is an agonist that interacts with at least one of said amino acid residues.

110. (New) The method of Claim 24 wherein the atomic structural model additionally comprises coordinates of amino acid residues that correspond to human estrogen receptor α residues Met343, Leu346, Gly 521, His524, Leu525, and either residues Met421 and Met528, or residues Met388 and Ile424, wherein said residues lie on a surface of a binding pocket in the ligand binding domain, and wherein said test compound is an agonist that interacts with at least one of said amino acid residues.

111. (New) The method of claim 24 wherein the atomic structural model is experimentally derived.

112. (New) The method of claim 111 wherein the atomic structural model has a resolution of at least 2.03 Å.

113. (New) The method of claim 24 wherein the atomic structural model has coordinates presented in Appendix 1.

114. (New) The method of claim 24 wherein the atomic structural model is of a homolog of the portion of the estrogen α receptor ligand binding domain, wherein the homolog comprises a ligand binding domain that has a root mean square deviation of not more than 1.5 Å from the backbone atoms of the amino acid residues of the atomic structural model of Appendix 1.

115. (New) A method for identifying an antagonist of ligand binding to an estrogen receptor, the method comprising:

modeling a test compound which fits spatially into an atomic structural model of the estrogen receptor α ligand binding domain, wherein the atomic structural model comprises atomic coordinates of helix 12 of the ligand binding domain, and atomic coordinates of a coactivator binding site, and further comprises atomic coordinates of a coactivator bound to the coactivator binding site; and

screening in an assay for estrogen receptor activity a compound which decreases the activity of the estrogen receptor by binding the ligand binding domain of the estrogen receptor, thereby identifying an agonist of ligand binding.

116. (New) The method of Claim 115 wherein the atomic structural model additionally comprises coordinates of amino acid residues that correspond to human estrogen receptor α residues Met343, Leu346, Ala350, Glu353, Leu384, Leu387, Leu391, Arg394, Phe404, Met421, Leu428, Gly521, His524, Leu525 and Met528, and wherein said test compound interacts with at least one of said amino acid residues.

117. (New) The method of Claim 115 wherein said screening is in vitro.

118. (New) The method of Claim 117 wherein said screening is high throughput screening.

119. (New) The method of Claim 115 wherein said test compound is from a library of compounds.

120. (New) The method of Claim 115 wherein the test compound is an antagonist that causes a change in position of helix 12 so that helix 12 contacts the coactivator binding site thereby inhibiting coactivator binding.

121. (New) The method of Claim 115 wherein the test compound is an antagonist that permits helix 12 to bind to a static region of the coactivator binding site.

122. (New) The method of Claim 115 wherein the modeling comprises providing the atomic coordinates of the portion of the estrogen receptor α ligand binding domain to a computerized modeling system.

123. (New) The method of Claim 115 wherein the atomic structural model additionally comprises coordinates of amino acid residues that correspond to human estrogen receptor α residues Met343, Leu346, Thr347, Ala350, Trp383, Leu384, Leu387, and Leu525, wherein said residues lie on a surface of a binding pocket in the ligand binding domain, and wherein said test compound is an antagonist that interacts with at least one of said amino acid residues.

124. (New) The method of Claim 115 wherein the atomic structural model additionally comprises coordinates of amino acid residues that correspond to human estrogen receptor α residues Met343, Leu346, Met421, Ile 424, Gly 521, His524, and Leu525, wherein said residues lie on a surface of a binding pocket in the ligand binding domain, and wherein said test compound is an antagonist that interacts with at least one of said amino acid residues.

125. (New) The method of claim 115 wherein the atomic structural model is experimentally derived.

126. (New) The method of claim 125 wherein the atomic structural model has a resolution of at least 2.03 Å.

127. (New) The method of claim 115 wherein the atomic structural model has coordinates presented in Appendix 1.

128. (New) The method of claim 115 wherein the atomic structural model is of a homolog of the portion of the estrogen α receptor ligand binding domain, wherein the homolog comprises a

ligand binding domain that has a root mean square deviation of not more than 1.5 Å from the backbone atoms of the amino acid residues of the atomic structural model of Appendix 1.

129. (New) The method of claim 115 wherein the modeling further comprises comparing a second atomic structural model of a portion of the estrogen receptor α ligand binding domain with the atomic structural model, wherein the second atomic structural model comprises atomic coordinates of amino acid residues of helix 12 of the ligand binding domain and of a coactivator binding site, wherein the helix 12 contacts the coactivator binding site, and further comprises atomic coordinates of an antagonist molecule bound to the ligand binding domain.

130. (New) The method of claim 129 wherein the second atomic structural model is experimentally derived.

131. (New) The method of claim 130 wherein the second atomic structural model has a resolution of at least 1.90 Å.

132. (New) The method of claim 129 wherein the second atomic structural model has coordinates presented in Appendix 2.

133. (New) The method of claim 129 wherein the second atomic structural model is of a homolog of the portion of the estrogen α receptor ligand binding domain, wherein the homolog comprises a ligand binding domain that has a root mean square deviation of not more than 1.5 Å from the backbone atoms of the amino acid residues of the atomic structural model of Appendix 2.

134. (New) A method of modulating estrogen receptor activity in a mammal by administering to a mammal in need thereof a sufficient amount of a compound that fits spatially and preferentially into an atomic structural model of a ligand binding domain of the estrogen receptor wherein said compound is designed so that binding of a coactivator to a coactivator binding site on the ligand binding domain is affected.

135. (New) The method of claim 134 wherein said compound is an antagonist and binding of a coactivator is inhibited.

136. (New) An isolated and purified protein complex comprising:

an estrogen receptor ligand binding domain;

a ligand bound to the ligand binding domain of the receptor; and
a coactivator bound to a coactivator binding site of the receptor.

137. (New) The isolated and purified protein complex of claim 136, wherein said coactivator is a peptide that comprises a motif whose sequence is LXXLL, wherein X is any amino acid residue.

138. (New) The isolated and purified protein complex of claim 137, wherein said coactivator is a GRIP1 peptide.

139. (New) An isolated and purified polypeptide consisting of a portion of the human estrogen receptor starting at amino acid residue 305 and ending at amino acid residue 549, as set forth in SEQ ID NO: 27 or SEQ ID NO: 28, bound to a ligand, and bound to a coactivator.

140. (New) A method of identifying a compound that modulates nuclear receptor activity, the method comprising:

screening a test compound in an assay characterized by binding of a test compound to the ligand binding domain of the nuclear receptor, wherein the test compound has been modeled by spatially fitting an atomic model of the test compound into an atomic structural model of a portion of the estrogen receptor ligand binding domain, wherein said atomic structural model comprises atomic coordinates of amino acid residues of the estrogen receptor coactivator binding site and coordinates of a molecule bound to the coactivator binding site, thereby identifying a test compound that modulates nuclear receptor activity.

141. (New) A method of identifying a compound that modulates estrogen receptor activity, the method comprising:

screening a test compound in an assay characterized by binding of a test compound to the ligand binding domain of the estrogen receptor, wherein the test compound has been modeled by spatially fitting an atomic model of the test compound into an atomic structural model of a portion of the estrogen receptor ligand binding domain, wherein said atomic structural model comprises atomic coordinates of amino acid residues of the estrogen receptor coactivator binding site and coordinates of a molecule bound to the coactivator binding site, thereby identifying a test compound that modulates estrogen receptor activity.